REMARKS

The Office Action of March 1, 2002 has been received and carefully reviewed. It is submitted that, by this Amendment, all bases of rejection and objection are traversed and overcome. Upon entry of this Amendment, Claims 1-20, 22, 23, 25-38 and 40-47 remain in the application. New claims 48-51 have been added in order to set forth additional specific embodiments of Applicant's invention. Reconsideration of the claims as amended is requested.

Claims 23-38 and 40-47 stand rejected under 35 U.S.C. 112, first paragraph, as the Examiner asserts that the specification does not reasonably provide enablement for any and all three-dimensional crosslinked hydrogel systems wherein any and all hydrophilic polymers are crosslinked using any and all cations.

By this Communication, Applicant has revised the relevant claims to recite that the hydrophilic polymer comprises an alginate salt, and that the cation is calcium. It is submitted that this obviates the Examiner's 112, first paragraph rejection. However, it is to be understood that Applicant does not intend to acquiesce to the Examiner's 112 first paragraph rejection, and reserves the right to pursue claims commensurate in scope with those pending before this or prior revision(s) of the subject claims.

Applicant would like the Examiner to note, however, that Applicant did not revise claims 42 or 43, as these claims depended from claims which recited alginate(s) and calcium. As such, Applicant requests that the 112, first paragraph rejection of claims 42 and 43 be withdrawn.

Applicant strongly takes issue with a statement made on page 4 of the March 1, 2002 Office Action. In the second full paragraph of that page, the Examiner attempts to discern the state of the art at the time of filing. **The references the Examiner cited as reflecting the state of the art at the time of filing postdate the priority date of the present application; and thus are incapable of teaching the state of the art at the time of filing.** The present application claims the benefit of provisional application S.N. 60/075,802, filed **February 24, 1998**. The "state of the art" documents cited by the Examiner (one of which is Applicant's own **subsequent publication**) are dated June 1998 (4 months after the underlying provisional

application was filed) and 2001 (3 years after the underlying provisional application was filed). As such, these references are irrelevant to prosecution of the present application. Further, Applicant respectfully requests that the Examiner retract his discussion on page 4 in the present Office Action of control of gelation rate, taken from Applicant's own 2001 jointly authored paper (with Catherine Kuo), as this teaching is irrelevant to prosecution of the present application claiming priority to February 24, 1998.

Claims 1-20, 22-38 and 39-47 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner states that in claims 1, 11, 23 and 34, it is unclear whether the "medium into which the hydrogel system is introduced" is different from the "medium or mixture into which the three-dimensional hydrogel cross-linking was performed."

Applicant fails to see the language "medium or mixture into which the three-dimensional hydrogel cross-linking was performed" in any of claims 1, 11, 23 or 34. In each of these claims, the medium is first introduced by the article "a," and appears after the hydrogel/hydrogel system is formed. As such, it is submitted that there is no lack of clarity between the mixture to which is added a calcium releasing compound to form the hydrogel/hydrogel system, and the medium into which the thus formed hydrogel/hydrogel system is introduced.

As such, it is submitted that the 112, second paragraph rejection has been traversed and overcome.

Claims 1-20, 22-38 and 40-47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Draget et al (1991) in view of Martinsen et al. (1989), further in view of Hauselmann et al (US Patent 5,658,343) and Cao et al (1996).

As to Draget, Hauselmann and Cao, the Examiner repeated his rejections from previous Office Actions. As to Martinsen, the Examiner states that this reference teaches evaluation of stability of Ca-alginate gel beads towards Na+ ions by transferring gel beads to solutions containing different concentrations of $CaCl_2$ and measuring the bead volume (shrinkage) every 24 hours for 3 days. The Examiner further states that Martinsen teaches that gel strength and shrinkage is the function of $CaCl_2$ concentration and gelling time (Page 84, col. 1-2, Figs. 7 and 8). In addition,

the Examiner states that Martinsen teaches that high gel strength, low shrinkage, high stability towards Na+ ions and high permeability of alginates are the most advantageous factors for the immobilization of living cells.

As such, the Examiner concludes that it would have been obvious in view of Martinsen to control the hydrogel shrinkage or swelling by transferring the hydrogels into solutions that contain different concentration of calcium ions.

None of the cited references teach or suggest **selective** size control of a three dimensional hydrogel system by varying cation concentration of a medium into which it is introduced. Draget is silent as to transferring a hydrogel into a medium.

The '343 patent controls the hydrogel system by a mechanical means (the boundary layers). The passage referred to by the Examiner (Col. 7, lines 29 et seq.) speaks of molar ratio of calcium ions to carboxyl groups in the gel to determine the amount of crosslinking--in sharp contrast, Applicant's invention as defined in claims 1, 11 and 23 recites selective control of the hydrogel system by varying cation/calcium ion concentration in the medium into which the hydrogel is introduced.

Martinsen, which was cited by Applicant in the present application, is an example of a traditional means of creating alginate gel beads. 1) Beads are the only structure which can be formed by Martinsen's method; this is in sharp contrast to Applicant's inventive hydrogel as defined in the pending claims, which may take any three dimensional shape. 2) The Martinsen beads are formed by allowing droplets of sodium alginate solution to fall into an aqueous solution of $CaCl_2$; this is in sharp contrast to Applicant's method as defined in relevant pending claims, Applicant's hydrogel is **not** formed in a calcium **solution**. 3) The crosslinking density of the Martinsen-formed beads is NOT uniform–the surface is highly crosslinked, and the interior has a low (if any) crosslinking density (this is known in the art); this is also in sharp contrast to Applicant's inventive hydrogel as defined in the pending claims, which is uniformly crosslinked and is structurally homogeneous. Since Applicant's hydrogels are not formed in calcium solutions, the inventive hydrogels do not have a layer (shell) of surface crosslinking, and are therefore open pored, thus calcium ions can move in and out of the hydrogel.

In Figs. 9 and 10 of Martinsen, the authors were studying how calcium competes with sodium, and how stable the gel beads were. (Figs. 7 and 8 of

Martinsen are irrelevant to Applicant's recitation of selectively controlling shrinking, swelling or maintaining of the hydrogel system by varying a calcium ion concentration of a medium into which the hydrogel system is introduced–Figs. 7 and 8 speak to the calcium chloride concentration of the solution used for gelation.) This is very different from Applicant's selective control of the size of the hydrogel/hydrogel system. Martinsen at p. 89, Col. 1, states that "[a]s a result, when calcium ions are present in sufficient amounts to counterbalance the osmotic pressure in the gel (Fig. 8), and to saturate the binding sites despite the competition from sodium ions (Fig. 10), and after binding has proceeded to a maximum on the time scale (Fig. 12), further physical changes are small in the gel system. (emphasis added)

As can be seen, Martinsen is NOT describing selective control of the size of a hydrogel–as quoted above, once all the binding sites (at the surface) are full, "further physical changes are small." However, in sharp contrast, Applicant can selectively cause the inventive hydrogel to swell, shrink or maintain by varying a calcium ion concentration of a medium into which the hydrogel system is introduced.

In summary regarding Martinsen: a) the composition and structure of the Martinsen hydrogel beads is quite different from the three dimensional, uniformly crosslinked and structurally homogeneous hydrogel system of Applicant's invention as defined in the claims; b) Martinsen's aim in Figs. 9 and 10 was to study competition between sodium and calcium ions; and c) Martinsen admits that after surface binding sites are full, physical changes are small.

Due to the disparity between Martinsen's hydrogel beads and Applicant's hydrogel, the skilled artisan would **not** have been taught and/or led to believe by Martinsen that if he placed Applicant's structurally homogeneous, three dimensional hydrogel (NOT formed in a calcium solution) in Martinsen's 0.9% NaCl solution, that he would be able to selectively control the shrinking, swelling or maintaining of Applicant's hydrogel by varying the concentration of the $CaCl_2$. In fact, Martinsen was published in 1989, and researchers in tissue engineering have been searching for a means of controlling the size of a formed hydrogel; however, prior to Applicant's invention as defined in the pending claims, the efforts had been unsuccessful. This would lead one to believe that Martinsen did NOT teach what the Examiner is asserting the publication taught.

It is further submitted that the Examiner is using hindsight to assume that Martinsen was teaching volume control of a non-bead, uniformly crosslinked hydrogel. The Examiner assumes that **different** hydrogel structures, formed by **different** methods will react the **same** in calcium ion solutions. Yet, the Examiner cites no evidence to buttress this theory. This assertion by the Examiner flies in the face of the oft-cited maxim that chemistry is an "unpredictable" art.

As such, it is submitted that Applicant has rebutted the Examiner's case of prima facie obviousness.

For all the above reasons, it is submitted that Applicant's invention as defined in independent claims 1, 11, 23 and 34, as well as all claims dependent therefrom, is not anticipated, taught or rendered obvious by Draget, Martinsen, Cao or '343, either alone or in combination, and patentably defines over the art of record.

In summary, Claims 1-20, 22, 23, 25-38 and 40-47 remain in the application. Claims 23, 25, 26, 29, 31, 34, 35, 40, 46 and 47 have been amended. Claim 24 has been canceled. New claims 48-51 have been added in order to set forth additional specific embodiments of Applicant's invention. It is submitted that, through this amendment, Applicant's invention as set forth in these claims is now in a condition suitable for allowance.

Further and favorable consideration is requested. If the Examiner believes it would expedite prosecution of the above-identified application, he is cordially invited to contact Applicant's Attorney at the below-listed telephone number.

Respectfully submitted,

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VERSION OF CLAIM AMENDMENTS WITH MARKINGS TO SHOW CHANGES MADE

23. (Three Times Amended) A method for preparing a three-dimensional hydrogel system, the method comprising the steps of:

adding a [cation-releasing] calcium-releasing compound to a mixture of at least one hydrophilic polymer comprising an alginate salt and a source of calcium cations to provide a three-dimensional crosslinked hydrogel system; and

selectively controlling shrinking, swelling or maintaining of the hydrogel system by varying a [cation] calcium ion concentration of a medium into which the hydrogel system is introduced[, wherein the cation in the medium is selected to be the same cation as the cation in the hydrogel system].

Please cancel claim 24 without prejudice.

25. (Amended) The method as defined in claim [24] 23 wherein the alginate salt is selected from the group consisting of sodium alginate and potassium alginate.

26. (Amended) The method as defined in claim [24] 23, wherein the source of calcium ions is selected from the group consisting of calcium carbonate, calcium sulfate, and calcium sulfate dihydrate.

29. (Amended) The method as defined in claim [24] 23 wherein the three-dimensional crosslinked hydrogel system has a calcium ion to carboxyl molar ratio ranging between about 0.09 and about 0.9.

31. (Twice Amended) The method as defined in claim [24] 23 wherein the cation in the medium is calcium ion.

34. (Three Times Amended) A three-dimensional crosslinked hydrogel composition, consisting essentially of:

at least one hydrophilic polymer comprising an alginate salt;

a source of calcium cations;

a [cation-releasing] calcium-releasing compound, whereby a mixture of the at least one hydrophilic polymer, the source of calcium cations and the [cation-releasing] calcium-releasing compound forms the crosslinked hydrogel composition; and

a culture medium into which the hydrogel composition is introduced, the culture medium having a predetermined [cation] calcium ion concentration, wherein the predetermined [cation] calcium ion concentration determines the shrinking, swelling or maintaining of the crosslinked hydrogel composition.

35. (Amended) The composition as defined in claim 34, wherein the [hydrophilic polymer is an] alginate salt is selected from the group consisting of sodium alginate and potassium alginate; wherein the source of calcium cations is [a source of calcium ions] selected from the group consisting of calcium carbonate, calcium sulfate, and calcium sulfate dihydrate; and wherein the [cation-releasing] calcium-releasing compound is D-glucono-δ-lactone.

40. (Twice Amended) The composition as defined in claim 34 wherein [the cation in the medium is calcium, and wherein] when the predetermined [cation concentration is a] calcium ion concentration is between about 0.0020 M and about 0.0030 M, the hydrogel composition remains substantially the same size.

46. (Amended) The three-dimensional crosslinked hydrogel composition as defined in claim 34 wherein [the cation in the medium is calcium, and wherein] when the predetermined [cation concentration is a] calcium ion concentration is between about 0.0005 M and about 0.0010 M, the hydrogel composition swelled.

47. (Amended) The three-dimensional crosslinked hydrogel composition as defined in claim 34 wherein [the cation in the medium is calcium, and

wherein] when the predetermined [cation concentration is a] calcium ion concentration is [of] about 0.0040 M, the hydrogel composition shrank.

48. (New) The method as defined in claim 1 wherein the three-dimensional crosslinked hydrogel system is structurally homogeneous.

49. (New) The three-dimensional crosslinked hydrogel composition as defined in claim 34 wherein the composition is structurally homogeneous.

50. (New) The method as defined in claim 1 wherein the source of calcium ions is in powder form.

51. (New) The three-dimensional crosslinked hydrogel composition as defined in claim 34 wherein the source of calcium cations is in powder form.